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(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract

A pharmaceutical composition for topical administration, including, as the pharmaceutically active component, at least 5 % by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof; an acid in an amount to completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof; a solvent composition including at least two of water, a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10 % by weight.

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PHARMACEUTICAL COMPOSITION

Background of the invention

The present invention relates to a vehicle system for a pharmaceutical composition comprising a piperidinopyrimidine derivative. More particularly minoxidil and to a pharmaceutical composition incorporating the vehicle system. Minoxidil is a pharmaceutically active ingredient having several indications including use as a hair growth stimulant.

Minoxidil has poor solubility in water and ethanol and pharmaceutical preparations currently marketed only contain a small percentage of minoxidil. That is, below 5%.

Numerous formulations comprising minoxidil have been published in the prior art including United States patents 4,139,619, 4,820,512, 5,104,646, 5,225,189, 4,938,953, 4,596,812, 5,006,332, 5,156,836 and 5,643,942. Many of the formulations require (or would require where the amount of minoxidil is greater than 5%) a very high percentage (often in the range of 30 to 50%) of propylene glycol or a similar glycol product in order to improve the solubility of minoxidil. Due to the viscosity and tack of propylene glycol, large amounts of propylene glycol or similar agents in a composition are not pharmaceutically or cosmetically elegant and may be unacceptable to the consumer. In addition, high concentrations of propylene glycol may cause local irritation and hypersensitivity upon application to the scalp.

It would accordingly be a significant advance in the art if a composition could be provided which would permit the inclusion of an increased percentage of the active ingredient, but without the disadvantages associated with a high propylene glycol concentration.

Accordingly, it is an object of the present invention to overcome, or at least alleviate, one or more of the difficulties and deficiencies related to the prior art. These and other objects and features of the present invention will be clear from

the following disclosure.

Summary of the invention

Accordingly, the present invention in a first aspect provides a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight.

Applicants have surprisingly discovered that by adjusting the acid concentration of the composition the solubility of the piperidinopyrimidine derivatives may be significantly increased without the necessity of utilising large amounts of propylene glycol or optionally by excluding propylene glycol altogether. Accordingly the total amount of active in the composition may be significantly increased. In a preferred form, the pharmaceutically active component is present in amounts of approximately 5 to 25% by weight, preferably approximately 5 to 15% by weight, more preferably approximately 7.5 to 12% by weight.

Preferably the piperidinopyrimidine derivative is minoxidil. Preferably the minoxidil is present in the form of a salt. The salt may include acetate, citrate, succinate, benzoate, hydrochloride, sulphate, phosphate or lactate. Preferably an acetate or lactate salt of minoxidil is used. The acetate or lactate salts may exhibit enhanced solubility and improve the ability to incorporate increased amounts of the active component in the composition.

In a preferred form the acid is added in an amount sufficient to provide an

apparent pH to the composition of approximately 7.0 or less. The apparent pH of the composition is preferably between approximately 5.0 to 7.0, more preferably between 6.0 to 6.5. Any suitable acid may be used to adjust the pH, including mineral acids, such as hydrochloric acid, sulphuric acid, nitric acid and phosphoric acid, or organic acids such as citric acid, acetic acid, succinic acid, or maleic acid, or mixtures thereof. Acetic acid or lactic acid is preferred.

In a preferred form the acid is present at a level that provides at least 0.01 Normal acid. Alternatively, the acid is present in an amount equal to, or greater than, the amount of the piperidinopyrimidine derivative in Normal amounts.

Preferably the lower alcohol is ethanol. The ratio of water to ethanol is preferably from approximately 9:1 to 1;9, more preferably approximately 1:1 to 1:3, by volume.

Preferably, the co-solvent includes benzyl alcohol. The benzyl alcohol may be present in amounts of approximately 2.5 to 95% by weight, preferably approximately 5 to 40% by weight, based on the total weight of the pharmaceutical composition.

Alternatively, or in addition the co-solvent may include a polyhydric alcohol, for example a polyol selected from the group consisting of 1,3-butylene glycol, propylene glycol, preferably glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400), hexylene glycol and dipropylene glycol, or glycerol. When propylene glycol is present, it may be present in amounts of approximately 10% by weight or less, preferably approximately 5% by weight, or less.

In compositions comprising 5% of minoxidil or greater, it is preferred to include benzyl alcohol in the composition. The benzyl alcohol may be present in amounts of up to 85% by weight, based on the total weight of the pharmaceutical composition.

In a preferred form the co-solvent system includes water and benzyl alcohol wherein the benzyl alcohol is in an amount of approximately 40 to 100% by

weight, based on the total weight of the co-solvent system.

In a preferred form the water is present in an amount no greater than 60% by weight.

In a preferred aspect, the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

The final presentation of the composition may be any suitable topical pharmaceutical preparation and may include solutions, lotions, ointments, mousses, foams, sprays, aerosols, shampoos and/or conditioners, gels, creams, pastes, and other preparations known in the art. The composition may also include other ingredients such as preservatives, buffers, stabilisers, propellants and the like.

Preferably the pharmaceutical composition is a mousse composition. The mousse composition may include a suitable propellant, for example hydrocarbons or chlorofluorocarbons. Alternatively the pharmaceutical composition may be a gel composition. The gel composition may include a suitable gelling agent, e.g. a cellulose derivative. A hydroxy propyl cellulose, for example that sold under the trade designation Klucel M, has been found to be suitable.

Where an aerosol formulation is used, the aerosol formulation may be a homogeneous, aqueous-alcoholic emulsion system. The aerosol formulation upon actuation produces a stabilized, homogeneous, expandable foam which breaks easily with shear. A composition of this type is sometimes referred to as a "mousse".

In a further preferred aspect, the pharmaceutical composition according to

the present invention may further include an effective amount of a skin penetrating agent.

Suitable skin penetrating agents include alcohols such as dodecanol and oleyl alcohol; amines, such as isopropyl amine, diisopropyl amine, triethyl amine, triethanol amine, diisopropanolamine and ethylene diamine; carboxylic acids, such as oleic acid, linoleic acid and linolenic acid; esters, such as dibutyl sebacate, dibutyl phthalate, butyl benzoate and ethyl caprate; and others, such as Azone, N methyl pyrollidone, bile salts and urea.

All of the compositions herein may be actuated using propellants known per se in the pharmaceutical or cosmetic fields. Such propellants include hydrocarbons such as propane, isobutane or dimethyl ether and chlorofluorocarbons such as P-12, P114, and a 40:60 mixture thereof.

In the pharmaceutical composition according to the present invention, in addition to the above essential components, general purpose components ordinarily used in hair treatment compositions can be formulated, within a range which does not impair the effect of the present invention, including vitamins such as vitamin B.sub.6, vitamin E and derivatives thereof, and biotin; hair generating agents or hair generating aids such as panthothenic acid and derivatives thereof, glycylrrhetic acid and derivatives thereof, nicotinic acid esters such as benzyl nicotinate, cyclosporins, carpronium chloride, cepharanthine, oxendolone, diazoxide, minoxidil, and ethynylesteradiol; antibacterial agents such as hinokitiol, hexachlorophen, phenol, benzalkonium chloride, cetylpyridinium chloride, undecylenic acid, trichlorocarbanilide, and bithionol; refrigerants such as menthol; drugs such as salicylic acid, zinc and derivatives, thereof, and lactic acid and alkyl esters thereof; amino acids such as arginine; oil components such as olive oil, squalane, fluid paraffin, isopropyl myristate, higher fatty acids, and higher alcohols; perfumes; antioxidants; UV-ray absorbers; dyes; humectants; thickeners; perfumes; colour additives and the like.

In a still further aspect of the present invention, there is provided a method for the treatment of hair loss and related indications in humans, which method

includes

providing

a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight; and

applying topically to the human scalp a therapeutically or prophylactically effective amount of the pharmaceutical composition.

The hair loss may be related to any of the forms of alopecia including male pattern alopecia. Related indications may include weakening of hair strength, loss of hair colour and the like.

Preferably the pharmaceutically active component includes a minoxidil or a minoxidil salt, more preferably a minoxidil acetate, succinate or citrate salt.

More preferably the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

The present invention will now be more fully described with reference to the accompanying figures and examples. It should be understood, however, that the

description following is illustrative only and should not be taken in any way as a restriction on the generality of the invention described above.

In each of the following examples it was necessary to add an appropriate amount of acid to ensure equivalent acid normality. The standard technique for such an adjustment is to measure the apparent pH of the solution.

In the examples, the apparent pH of each formulation was measured once prepared. The measured taken as the apparent pH due to the high proportion of organic modifiers in the formulations. Typically, 0.5% (w/w) glacial acetic acid (0.1M) would be used in the formulation, which would equate to a pH of 1.0 in an aqueous system when no other components are contributing to the pH of the solution.

EXAMPLE 1

Topical Minoxidil lotion 5% with no propylene glycol

Minoxidil	5.00%
Ethanol	60.3%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	0.6
Purified Water	to total 100%

The apparent pH of the final formulated solution was measured at 6.24.

EXAMPLE 2

Topical Minoxidil mousse 5% for hair treatment

Minoxidil	5.00%
Cetyl Alcohol	2.20%
Stearyl Alcohol	1.00%
Ethanol	51.8
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Propylene Glycol	5.00%
Propellant P75	4.30%
Acetic Acid	qs. pH 6.0
Purified water	to total 100%

EXAMPLE 3

Topical Minoxidil lotion 8% for hair treatment

Minoxidil	8.00%
Ethanol	50.50%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Nitric Acid	qs. pH 6.0
Propylene Glycol	7.30%
Benzyl Alcohol	5.00%
Purified Water	to total 100%

EXAMPLE 4

Topical 8% (w/w) Minoxidil solution

Minoxidil	8.0%
Ethanol	50.5%
Crilet 3	0.4%
Teric 12A4	1.0%
Glacial Acetic Acid	0.3%
Propylene Glycol	7.5%
Benzyl Alcohol	5.0%
Purified Water	to total 100%

The apparent pH of the final formulated solution was measured at 6.24.

EXAMPLE 5

Topical Minoxidil lotion 10% for hair treatment

Minoxidil	10.00%
Ethanol	48.0%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Propylene Glycol	10.0%
Benzyl Alcohol	5.00%
Purified Water	to total 100%

EXAMPLE 6

Topical Minoxidil lotion 10% for hair treatment

Minoxidil	10.00%
Ethanol	47.50%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	15.00%
Purified Water	to total 100%

EXAMPLE 7

Topical 10% (w/w) Minoxidil solution

	Formulation 3a	Formulation 3b
Minoxidil	10.00%	10.00%
Ethanol	46.80%	44.20%
Crillet 3	0.4%	0.4%
Teric 12A4	1.0%	1.0%
Glacial Acetic Acid	1.0%	0.3%
Propylene Glycol	10.0%	nil
Benzyl Alcohol	5.00%	2.00%
Purified Water	to total 100%	to total 100%

The apparent pH of the final formulated solutions was measured at 6.0 and 6.5 for formulations 3a and 3b, respectively.

EXAMPLE 8

Topical Minoxidil lotion 11% for hair treatment

Minoxidil	11.00%
Ethanol	44.20%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	20.00%
Purified Water	to total 100%

EXAMPLE 9

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	20.00%
Purified Water	to total 100%

EXAMPLE 10

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	10.00%
Propylene Glycol	10.00%
Purified Water	to total 100%

EXAMPLE 11

Topical Minoxidil lotion 12% for hair treatment

Minoxidil	12.00%
Ethanol	42.7%
Polysorbate 60	0.4%
Polyoxyethylene lauryl alcohol	1.00%
Acetic Acid	qs. pH 6.0
Benzyl Alcohol	15.00%
Propylene Glycol	5.00%
Purified Water	to total 100%

There appear to be no obvious gross stability issues associated with any of the formulations. The levels of minoxidil were assayed in formulations 1 and 3a after they had been stored for one and three months at 4°C and 50°C. No measurable loss in potency was observed.

An aqueous gel was prepared by adding 0.75% (w/w) Klucel M (hydroxypropyl cellulose) to Example 4. The viscosity of the gel was measured at

2400 cPoise at 20°C.

EXAMPLE 12

Investigations were carried out to determine which of the components present in Example 7 (10% (w/w) minoxidil solution) were contributing to the solubilisation of minoxidil. The investigation was split into three sections:

- Effect of Co-solvent
- Effect of pH
- Effect of Salt

The solubility determination involved preparation of saturated solutions of minoxidil in the media of interest. These solutions were then filtered (0.45 µm) and analysed against a standard curve by means of direct UV spectroscopy.

Aqueous unbuffered solubility of Minoxidil

The aqueous solubility of minoxidil was found to be 2.2 mg/mL.

Effect of Co-solvent

The solubility of minoxidil was determined in each of the co-solvents, benzyl alcohol, glycerol, propylene glycol and ethanol. Additionally, the solubility of minoxidil was determined in 10% (w/w) solutions of each of the co-solvents, ethanol, propylene glycol and glycerol in water. A 4% (w/w) solution of benzyl alcohol was used since this was found to be the limit of the solubility of benzyl alcohol in water. The following table summarises the results of these studies.

Sample	Minoxidil Solubility (mg/mL)
Benzyl alcohol	125.1
Glycerol	47.3
Propylene Glycol	86.9
Ethanol	18.8
10% (w/w) Ethanol/Water	3.4
10% (w/w) Propylene Glycol/Water	3.0
4% (w/w) Benzyl Alcohol/Water	4.5
10% (w/w) Glycerol/Water	2.7

Analysis indicated that of the systems studied only the use of pure benzyl alcohol would result in the desired 10% (w/w) minoxidil solution.

Effect of apparent pH

Attempts were made to prepare saturated solutions of minoxidil in acetate buffers at apparent pH's 2.5, 3.5, 4.6, 5.0 and 6.0. Saturated solutions were achieved with those pHs above the pKa of minoxidil (4.61), the results of which are summarised in the following table.

pH	Minoxidil Solubility (mg/mL)
6.0	2.5
5.0	4.1
4.6	11.3

It was not possible to determine the solubility limits of minoxidil at pH's below it's pKa, as minoxidil was found to be extremely soluble in acidic media and the buffer used had insufficient capacity to avoid the drift in pH observed with additions of minoxidil to the solution. The maximum minoxidil concentration studied was 22 mg/mL and was found to be completely soluble in pH 2.5 and 3.5 solutions at this concentration. The following table outlines the maximum solubility that would be expected in an acidic aqueous media knowing the solubility of the

base form of minoxidil is 2.2 mg/mL and assuming infinite solubility of the acid form of minoxidil.

pH	Minoxidil Solubility (mg/mL)
3.6	22.0
3.0	87.6
2.6	220.0
2.0	876.0

Effect of Salt

Minoxidil base was used for these studies with the appropriate salt (acetate or HCl) formed *in situ*. As discussed above the use of low pH acetate buffers significantly increased the solubility of minoxidil.

The major factors affecting the solubilisation of minoxidil in an aqueous environment were found to be:

The type and proportion of co-solvents present in the formulation

The pH of the final formulated solution

The amount of minoxidil used

The acid form of minoxidil has been shown to be much more soluble in an aqueous environment. The use of co-solvents has been shown to enhance the solubility of the minoxidil free base. The co-solvents may also enhance the solubility of the acid form. The use of an appropriate salt enhances the solubility of the acid form of minoxidil. Therefore, a combination of these three factors may be used to optimise the solubility of minoxidil in a topical solution based formulation.

All the above examples were stored at room temperature and no crystallisation or precipitation was observed for at least 10 days.

Please note all percentages are based upon the total weight of the

composition unless otherwise specified.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

It will also be understood that the term "comprises" (or its grammatical variants) as used in this specification is equivalent to the term "includes" and should not be taken as excluding the presence of other elements or features.

CLAIMS

1. A pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight.

2. A pharmaceutical composition according to Claim 1, wherein the acid is added in an amount sufficient to provide an apparent pH to the composition of approximately 7.0 or less.

3. A pharmaceutical composition according to Claim 1, wherein the pharmaceutically active component is present in an amount of from approximately 5 to 25% by weight, based on the total weight of the pharmaceutical composition.

4. A pharmaceutical composition according to Claim 3, wherein the pharmaceutically active component is present in an amount of approximately 7.5 to 12% by weight, based on the total weight of the pharmaceutical composition.

5. A pharmaceutical composition according to Claim 1, wherein the pharmaceutically active component is minoxidil or a salt thereof.

6. A pharmaceutical composition according to Claim 2, wherein the acid provides to the composition an apparent pH in the range of approximately 5.0 to 7.0.

7. A pharmaceutical composition according to Claim 2, wherein the acid is a

mineral or organic acid.

8. A pharmaceutical composition according to Claim 7, wherein the acid includes acetic or lactic acid.

9. A pharmaceutical composition according to Claim 1, wherein the solvent composition includes water and ethanol in a range of approximately 1:1 to 1:3 by volume.

10. A pharmaceutical composition according to Claim 1, wherein the co-solvent includes benzyl alcohol.

11. A pharmaceutical composition according to Claim 1, wherein the solvent composition system includes water and benzyl alcohol wherein the benzyl alcohol is in an amount of approximately 40 to 100% by weight based on the total weight of the co-solvent system.

12. A pharmaceutical composition according to Claim 1, wherein the water is present in an amount no greater than approximately 60% by weight based on the total weight of the co-solvent system.

13. A pharmaceutical composition according to Claim 1, wherein the co-solvent includes an alkylene glycol.

14. A pharmaceutical composition according to Claim 13, wherein the alkylene glycol is selected from one or more of the group consisting of glycerol, 1,3-butylene or propylene glycol.

15. A pharmaceutical composition according to Claim 1, wherein the acid is present at a level that provides at least 0.01 Normal acid.

16. A pharmaceutical composition according to Claim 1, wherein the acid is present in an amount equal to or greater than the amount of the piperidinopyrimidine derivative in Normal amounts.

17. A pharmaceutical composition according to Claim 1, wherein the solvent system includes water and ethanol in a range of approximately 9:1 to 1:9 by volume.

18. A pharmaceutical composition according to Claim 5, wherein the pharmaceutically active component is a minoxidil salt.

19. A pharmaceutical composition according to Claim 18, wherein the minoxidil salt is a minoxidil acetate or lactate salt.

20. A pharmaceutical composition according to Claim 1, including

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil acid salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

21. A method for the treatment of hair loss and related indications in humans, which method includes

providing

a pharmaceutical composition for topical administration, including, as the pharmaceutically active component,

at least 5% by weight, based on the total weight of the composition of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

an acid in an amount to substantially completely solubilise the piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof;

a solvent composition including a solvent selected from water and/or a lower alcohol and a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols; wherein when the co-solvent includes propylene glycol, it is present in an amount of less than approximately 10% by weight; and

applying topically to the human scalp a therapeutically or prophylactically

effective amount of the pharmaceutical composition.

22. A method according to Claim 21, wherein the pharmaceutically active component includes minoxidil or a minoxidil salt.

23. A method according to Claim 22, wherein the minoxidil salt is a minoxidil acetate or lactate salt.

24. A method according to Claim 21, wherein the pharmaceutical composition includes

approximately 5 to 12% by weight, based on the total weight of the composition, of a minoxidil or a minoxidil salt;

approximately 88 to 95% by weight of a solvent composition including

approximately 10 to 70% by weight of ethanol,

approximately 2.5 to 85% by weight of benzyl alcohol;

and less than 10% by weight, propylene glycol.

25. A pharmaceutical composition according to Claim 1, substantially as herein before described with reference to any one of the examples.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00294

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 031/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 031/505

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVE.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: minoxidil, acid
CAPLUS: minoxidil, acid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5183817A (BAZZANO) 2 February 1993 Column 24 lines 11-51.	1-25
X	US 4866067 (DI SCHIENA) 12 September 1989 Column 3.	1-25
X	WO 8302558A (BAZZANO) 4 August 1983 Page 8.	1-25

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 07048230A (JAPATIC ENGLISH LANGUAGE ABSTRACT) (HORIUCHI HIDEO et al) 21 February 1995.	1-25